REMARKS

I. Status of the Claims

Claims 251-287 and 625 were pending in the October 7, 2010 Office Action. With this Reply, claims 261, 271-274, 286 and 287 are amended. The claim amendments are made without prejudice or disclaimer and present no new matter. Claims 251-287and 625 are presented for reconsideration.

II. Information Disclosure Statement

Applicants provide herewith an Information Disclosure Statement (IDS), in compliance with 37 CFR 1.97 and 1.98, citing one reference. Applicants authorize the withdrawal of the fee under 37 CFR 1.17(p) for this IDS from Deposit Account 05-1135.

III. Claim Objection

Claim 261 is objected to as imprecisely describing the reverse transcriptases recited therein by using the phrase "with amounts of RNA." Applicants request withdrawal of this objection since the claim as amended precisely describes the transcriptases by amending the objectionable phrase to "capable of transcribing amounts of RNA" as suggested in the Office Action.

IV. Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 284, 286 and 287 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite as follows.

(a) Claim 284 is asserted to be indefinite for including a combination of T and U as a homopolymeric sequence. Claim 284 as amended recites "[[T]]he method of claim 251 wherein said sequences complementary to said homopolymeric sequences in said library of nucleic acid targets are comprised of T, U or any combination thereof." Since both T and U are complementary to a poly A sequence, the skilled artisan would

understand that the complement of a homopolymeric sequence can comprise T or U or any combination thereof. Withdrawal of this rejection is thus respectfully requested.

(b) Claims 286 and 287 are asserted to be indefinite as being confusing as to "whether the homopolymeric sequence is intended to refer to the homopolymeric sequence in the target nucleic acid or the homopolymeric portion of the primer that is complementary to the homopolymeric sequence in the target nucleic acid." Applicants respectfully request withdrawal of this rejection since the claims as amended are clear that the homopolymeric sequences referred to in both claims are primer or nucleic acid construct sequences.

V. Rejections under 35 U.S.C. § 103

(a) Claims 251, 252, 254,256, 259-264, 269-273, 275, 281, 285-287 and 625 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554) in view of Nam et al. (2002, Proc. Natl. Acad. Sci. USA 99:6152-6156) and in further view of Laird et al. (EP 1 201 768). Applicants request reconsideration and withdrawal of this rejection in light of the following comments.

Lin et al. is asserted to teach all elements of the claims except "...that the primers contain 3' terminal nucleotides that are substituted with nucleotide analogues having a modification at the 2' position of the ribose ring .... Lin also does not teach the use of chimeric primers ...." Office Action at p. 9. Laird et al. is asserted to teach "methods for conducting PCR amplification using modified primers" including 2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides (Office Action at pp. 9-10) and Nam et al. is asserted to provide motivation to combine Lin et al. and Laird et al. to apply the modified primers of Laird et al. to the primers of Lin et al. (Office Action at p. 29).

The Office Action asserts at p. 9 that Nam et al. provides the requisite motivation by teaching that "...oligo(dT) primers can produce spurious truncated amplification products during reverse transcription reactions due to their ability to hybridize to internal

polyA sequences contained in the mRNA template in addition to the polyA tail of the mRNA template...."

With regard to the above comments on the Nam et al., and Laird et al., references, we wish to first point out the nature of the problem that is being solved by the present pending claim. As noted in paragraph **[0031]** of the specification as published in US 2006/0057583, addition of a non-inherent UDT (as required by step (d) of the claim 251) can create problems.

> Although separation of the extended and unextended primers can be carried out by various physical means, there may still be some carryover of unextended primers. However since only the extended primers are desired to act as targets for the addition of non-inherent UDT in later steps, addition of a UDT sequence to unextended primers ... can be deleterious since these products can ultimately form non-target derived double-stranded transcription units.

The problem is then discussed in more detail in this passage with regard to promoter sequences and specific problematic events that result from addition of UDTs to unextended primers. In paragraph **[0032]**, the solution to this problem is described as the use of one or more nucleotides at the 3' end that are other than deoxyribonucleotides. Means of accomplishing this are the use of ribonucleotides discussed in paragraph **[0033]** and nucleotide analogues discussed in paragraph **[0035]**. Furthermore, Examples 2, 3 and 4 show the use of ribonucleotides at the 3' ends of primers and Examples 5, 6, 7 and 8 show the use of primers with analogues at the 3' ends.

In contrast to the problems posed in the specification and solved by the present invention discussed above, the Office Action cites Nam et al. as describing hybridization of primers to internal oligo A sequences and Laird et al. as disclosing non-target sequences (and primers) that are erroneously used as primer binding sites. Nam describes the use of one or two "anchored" nucleotides at the 3' end of a primer. Applicants note that the use of "anchored primers" is not recited in the instant claims.

With regard to Laird et al., Applicants note that the use of analogues as described in that reference was specifically discussed in paragraph **[0043]** of the instant specification as follows:

> "Nucleotide analogues at the 3' end of primers have been disclosed recently (US Patent Application nos. 2003/0044817 and 2003/0077609) to increase discrimination between target sequences and non-target sequences. However, in the present invention, for library amplifications where common sequences of a library of multiple species of nucleic acids are the targets for primer binding, **this discrimination is not as relevant** and the dual properties of a) discrimination between extended and unextended primers and b) increased synthesis of a a library, are the beneficial effects that are sought after and achieved by the use of the nucleotide analogues at the 3' end of primers."

(emphasis added). The '817 publication cited in the above quote is the US equivalent of Laird et al., i.e., EP 1201768 cited in the Office Action. As the above passage establishes, the problem of specificity that is solved by Laird et al. does not offer any particular advantages for the Lin et al. method, where there is essentially universal amplification of any and all sequences having a poly A tail. As such, there is no particular reason to utilize the Laird et al. primer design with the method of Lin et al. Thus, even if Nam is adapted for use with the method of Lin et al., there is no particular motivation to add the method of Laird et al. since the problems identified in Laird et al., primer-dimer formation and spurious expression results derived from priming at inappropriate sequences, are not problems in the method of Lin et al. It is only in the present application that particular benefits are shown to be endowed to a universal RNA amplification system for expression analysis by the presence of nucleotide analogues at the 3' end of primers. Thus, there is no reason to combine Lin et al. and Laird et al. because the problem identified in Laird et al. is not present in the Lin et al. method. Since there is no motivation to combine the cited references, the instant obviousness rejection has no basis. Withdrawal of this rejection is therefore respectfully requested.

(b) Claims 253, 255, 257 and 258 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (discussed under **(a)** above) in view of Nam et al.

(discussed under **(a)** above) and further in view of Laird et al. (discussed under **(a)** above) and in further view of Kutsu et al. (US 6,242,189). The Office Action asserts at p. 12 that the combination of Lim et al., Nam et al. and Laird et al. teach or suggest all elements of claims 253, 255, 257 and 258 except "...that the library of nucleic acid targets is comprised of copies of nucleic acids isolated from a biological sample ..." and "...adding a homopolymeric sequence to the library of nucleic acid targets using an enzyme, such as TdT, after isolation of the nucleic acids from the biological sample...." Applicants request reconsideration and withdrawal of this rejection in light of the following comments.

As discussed under **(a)** above, the combination of Lim et al., Nam et al. and Laird et al. do not teach or suggest the methods of parent claim 251 since that combination does not provide any motivation to utilize the modified nucleotides of Laird et al. in the method of Lin et al. to achieve the instant methods. Kutsu et al. also do not provide that motivation, since Kutsu et al. do not discuss modified terminal nucleotides for solving problems in methods of copying libraries using primers to homopolymeric sequences. Thus, the combination of Lim et al., Nam et al., Laird et al. and Kutsu et al. do not teach or suggest the claimed method. As such, those references do not render the instant claims obvious. Withdrawal of this rejection is therefore respectfully requested.

(c) Claims 265-268 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (discussed under **(a)** above) in view of Nam et al. (discussed under **(a)** above) and further in view of Laird et al. (discussed under **(a)** above) and in further view of Willis et al. (US 6,858,412) and further in view of Moran et al. (1996, Nucleic Acids Research 24:2044-2052). The Office Action asserts at p. 14 that the combination of Lim et al., Nam et al. and Laird et al. teach all elements of claims 265-268 except for "...a terminator nucleotide in the TdT tailing reaction...." Applicants request reconsideration and withdrawal of this rejection in light of the following comments.

As discussed under **(a)** above, the combination of Lim et al., Nam et al. and Laird et al. do not teach or suggest the methods of parent claim 251 since that combination does not provide any motivation to utilize the modified nucleotides of Laird et al. in the method of Lin et al. to achieve the instant methods. Neither Willis et al. nor Moran et al., alone or in combination with any of the other cited references, provide the lacking motivation since those references do not discuss modified terminal nucleotides for solving problems in methods of copying libraries using primers to homopolymeric sequences. Thus, the combination of Lim et al., Nam et al., Laird et al. and Willis et al. and Moran et al. do not teach or suggest the claimed method. As such, those references do not render the instant claims obvious. Withdrawal of this rejection is therefore respectfully requested.

(d) Claims 274 and 276 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (discussed under **(a)** above) in view of Nam et al. (discussed under **(a)** above) and further in view of Laird et al. (discussed under **(a)** above) and in further view of Sousa et al. (US 5,849,546). The Office Action asserts at pp. 16-17 that the combination of Lim et al., Nam et al., and Laird et al. teach or suggest all elements of claims 274 and 276 except for "...the use of a mutated RNA polymerase for generation of a chimeric RNA/DNA transcript...." Applicants request reconsideration and withdrawal of this rejection in light of the following comments.

As discussed under **(a)** above, the combination of Lim et al., Nam et al. and Laird et al. do not teach or suggest the methods of parent claim 251 since that combination does not provide any motivation to utilize the modified nucleotides of Laird et al. in the method of Lin et al. to achieve the instant methods. Sousa et al., alone or in combination with any of the other cited references, do not provide the lacking motivation since Sousa et al. do not discuss modified terminal nucleotides for solving problems in methods of copying libraries using primers to homopolymeric sequences. Thus, the combination of Lim et al., Nam et al., Laird et al. and Sousa et al. do not teach or

suggest the claimed method. As such, those references do not render the instant claims obvious. Withdrawal of this rejection is therefore respectfully requested.

(e) Claims 277, 278 and 280 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (discussed under **(a)** above) in view of Nam et al. (discussed under **(a)** above) and further in view of Laird et al. (discussed under **(a)** above) and in further view of Steffens et al. (1995, Genome Research 5:393-399). The Office Action asserts at p. 18 that the combination of Lim et al., Nam et al., and Laird et al. teach or suggest all elements of claims 277, 278 and 280 except for "...including labeled nucleotides in the final RT-PCR amplification step used to generate a copy of the RNA transcription product..." or specific examples of labeled nucleotides. Applicants request reconsideration and withdrawal of this rejection in light of the following comments.

As discussed under **(a)** above, the combination of Lim et al., Nam et al. and Laird et al. do not teach or suggest the methods of parent claim 251 since that combination does not provide any motivation to utilize the modified nucleotides of Laird et al. in the method of Lin et al. to achieve the instant methods. Steffens et al., alone or in combination with any of the other cited references, do not provide the lacking motivation since Steffens et al. do not discuss modified terminal nucleotides for solving problems in methods of copying libraries using primers to homopolymeric sequences. Thus, the combination of Lim et al., Nam et al., Laird et al. and Steffens et al. do not teach or suggest the claimed method. As such, those references do not render the instant claims obvious. Withdrawal of this rejection is therefore respectfully requested.

(f) Claim 279 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (discussed under **(a)** above) in view of Nam et al. (discussed under **(a)** above) and further in view of Laird et al. (discussed under **(a)** above) and in further view of Sousa et al. (discussed under **(d)** above) and in further view of Steffens et al. (discussed under **(e)** above). The Office Action asserts at p. 20 that the combination of

Lim et al., Nam et al., Laird et al. and Sousa et al. teach or suggest all elements of claims 279 except for specific examples of labels, which is provided by Steffens et al. Applicants request reconsideration and withdrawal of this rejection in light of the following comments.

As discussed under **(a)** above, the combination of Lim et al., Nam et al. and Laird et al. do not teach or suggest the methods of parent claim 251 since that combination does not provide any motivation to utilize the modified nucleotides of Laird et al. in the method of Lin et al. to achieve the instant methods. Sousa et al. and Steffens et al., alone or in combination with any of the other cited references, do not provide the lacking motivation since those references do not discuss modified terminal nucleotides for solving problems in methods of copying libraries using primers to homopolymeric sequences. Thus, the combination of Lim et al., Nam et al., Laird et al., Sousa et al. and Steffens et al. do not teach or suggest the claimed method. As such, those references do not render the instant claims obvious. Withdrawal of this rejection is therefore respectfully requested.

(g) Claims 282 and 283 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (discussed under **(a)** above) in view of Nam et al. (discussed under **(a)** above) and further in view of Laird et al. (discussed under **(a)** above) and in further view of Stinear et al. (1996, Applied and Environmental Microbiology 62:3385-3390). The Office Action asserts at p. 22 that the combination of Lim et al., Nam et al., and Laird et al. teach or suggest all elements of claims 282 and 283 except for "...the use of bead-immobilized primers..." which is taught by Stinear et al. Applicants request reconsideration and withdrawal of this rejection in light of the following comments.

As discussed under **(a)** above, the combination of Lim et al., Nam et al. and Laird et al. do not teach or suggest the methods of parent claim 251 since that combination does not provide any motivation to utilize the modified nucleotides of Laird et al. in the method of Lin et al. to achieve the instant methods. Stinear et al., alone or in

combination with any of the other cited references, do not provide the lacking motivation since that reference does not discuss modified terminal nucleotides for solving problems in methods of copying libraries using primers to homopolymeric sequences. Thus, the combination of Lim et al., Nam et al., Laird et al. and Stinear et al. do not teach or suggest the claimed method. As such, those references do not render the instant claims obvious. Withdrawal of this rejection is therefore respectfully requested.

(h) Claim 284 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (discussed under **(a)** above) in view of Nam et al. (discussed under **(a)** above) and further in view of Laird et al. (discussed under **(a)** above) and in further view of Petrick et al. (1997, Journal of Virological Methods 64:147-159). The Office Action asserts at p. 23 that the combination of Lim et al., Nam et al., and Laird et al. teach or suggest all elements of claims 284 except "...that the homopolymeric segment is comprised of U, T, or a combination thereof." Applicants request reconsideration and withdrawal of this rejection in light of the following comments.

As discussed under **(a)** above, the combination of Lim et al., Nam et al. and Laird et al. do not teach or suggest the methods of parent claim 251 since that combination does not provide any motivation to utilize the modified nucleotides of Laird et al. in the method of Lin et al. to achieve the instant methods. Petrick et al., alone or in combination with any of the other cited references, do not provide the lacking motivation since that reference does not discuss modified terminal nucleotides for solving problems in methods of copying libraries using primers to homopolymeric sequences. Thus, the combination of Lim et al., Nam et al., Laird et al. and Petrick et al. do not teach or suggest the claimed method. As such, those references do not render the instant claims obvious. Withdrawal of this rejection is therefore respectfully requested.

(i) Claim 625 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nam et al. (discussed under **(a)** above) in view of Laird et al. (discussed under **(a)** above). The Office Action asserts that Nam et al. teach all elements of the claim except

for the use of a 3' terminal nucleotide containing 2' substitutions. Applicants request reconsideration and withdrawal of this rejection in light of the following comments.

While claim 625 is directed to a method for synthesizing a copy of a nucleic acid target, Laird et al. teach the use of 3' terminal nucleotides with 2' substitutions only in the context of PCR amplification. The skilled artisan would understand that methods for PCR amplification, where multiple priming and extension procedures take place, is very different from a simple primer and extension procedures, and that the 3' terminal nucleotide containing 2' substitutions, while apparently useful for preventing nonspecific amplification, as taught by Laird et al., would not necessarily be useful or have any positive effect on the problem identified by Nam et al., *i.e.*, truncated cDNA production during reverse transcription. Indeed, the skilled artisan would understand that the 3' terminal nucleotide containing 2' substitutions would not likely be useful in that context, since the truncated cDNA problem identified by Nam et al. is due to the primer hybridizing to internal poly(A) sequences, which a primer having a 3' terminal nucleotide containing 2' substitutions would not prevent. Therefore, a skilled artisan wanting to avoid the problem identified in Nam et al. would not utilize primers having 3' terminal nucleotides containing 2' substitutions. As such, there would be no motivation to combine the methods of Nam et al. with Laird et al., since primers having 3' terminal nucleotides containing 2' substitutions would not solve the problem identified by Nam et al.

In light of the above discussion, it is clear that Nam et al. could not be combined with Laird et al. since the 3' terminal nucleotide containing 2' substitutions do not solve the problem identified by Nam et al. As such, those references do not render the instant claims obvious. Withdrawal of this rejection is therefore respectfully requested.

VI. Conclusion

In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejections of record and passage of the claims to allowance.

Applicants authorize the United States Patent and Trademark Office to charge all fees required to maintain pendency of this application, including the extension of time fee and Information Disclosure Statement fee, to Deposit Account No. 05-1135.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,

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